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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,830	12/28/1999	JEFFREY M. LEIDEN	2844/53802	1518

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/473,830	LEIDEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30,32,33 and 35-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30, 32, 33 and 35-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 2-9-04 has been entered. Claim 42 has been amended. Claim 47 has been added. Claims 24-30, 32, 33 and 35-47 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 41, 42, 44 and 46 remain rejected and claim 47 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of introducing an AAV vector expressing an angiogenic protein, such as FGF protein and VEGF protein, into cardiomyocytes via intracoronary injection so as to ameliorate the symptom of a hear disease as disclosed by Hammond et al., 1998 (WO 98/50079), does not reasonably provide enablement for a method of introducing an AAV vector expressing any protein or antisense RNA other than angiogenic protein into cardiomyocytes via intracoronary injection so as to provide therapeutic effect in vivo for a particular disease, such as hear disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 9-10-03. Applicant's arguments filed 2-9-04 have been fully considered but they are not persuasive.

The newly added claim 47 is directed to the method of claim 41 and specifies the anti-sense RNA is capable of inducing angiogenesis or in capable of inhibiting antiogenesis.

Applicants argue that the claims are directed to a delivery method of introducing nucleic acid into cardiomyoxyte via rAAV vector to provide stable and efficient transduction of those cells and do not require specific therapeutic effect to be obtained. Further, claim 46 only indicates what particular cardiovascular effect is achieved and not a particular level or degree of the effect (amendment, p. 6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-10-03. As discussed in the preceding Official action mailed 9-10-03, the specification states "The ability to stably and efficiently program recombinant gene expression in cardiomyocytes facilitates gene therapy approaches for a variety of cardiovascular disease and conditions" and "The present invention is directed to a method of treating a cardiovascular condition by infusing an rAAV vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably efficient transduce the cardiomyocytes perfused to the artery or sinus" (see specification, page 1, 3). The claims read on gene therapy *in vivo* for a variety of cardiovascular diseases and conditions in light of the specification as discussed above. Therefore, specific therapeutic effect for a particular disease or disorder in vivo is required for the claimed invention. Further, claim 46 specifies the desired molecule has an effect in inducing angiogenesis, inhibiting angiogenesis, stimulating or inhibiting cell proliferation, **treating restenosis, treating atherosclerosis, treating congestive heart failure, treating ischemic cardiomyopathy, and treating malignant arrhythmia**. Thus, specific therapeutic effect is expected in treating various disease in vivo as claimed.

Applicants argue that nonelement of the claims require a therapeutic effect for a particular cardiovascular disease in a patient in vivo and since nucleic acid encoding markers and angiogenic proteins can be introduced into the cells in vivo by the claimed method, there is no

reason to doubt that other nucleic acids can not be introduced into cells in vivo by the claimed method (amendment, p. 7). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and the reasons set forth above.

Applicants cite Dr. Phamacek's declaration and argue that method of making rAAV vector encoding a desired molecule was known in the art, effective transduction of various rodent, animals other than rodent, and human cells using rAAV vectors encoding markers and therapeutic proteins had been demonstrated, rAAV vectors had been used to express therapeutic effective amounts of several genes in the liver, brain, vasculature, and lungs of non-human animals, and the claimed invention is routine experimentation based on the teachings of the specification and the state of the art (amendment, p. 7-8). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and the reasons set forth above. As discussed above, the claims read on gene therapy *in vivo* for a variety of cardiovascular diseases and conditions in light of the specification. Therefore, specific therapeutic effect for a particular cardiovascular disease or disorder in vivo is required for the claimed invention. The claims encompass introducing an AAV vector expressing a desired molecule, such as an antisense RNA, an ion channel gene, a contractile protein, a beta-adrenergic receptor or kinase, a phospholamban, a thymidine kinase, p21, and p27 etc., into cardiomyocytes by infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm body weight so as to induce angiogenesis, inhibit angiogenesis, stimulate or inhibit cell proliferation, treat restenosis, treat atherosclerosis, treat congestive heart disease, treat ischemic cardiomyopathy, or treat malignant arrhythmia. The specification fails to provide adequate guidance and evidence whether the desired molecule would be expressed and be

present in a sufficient amount at the targeted site such that said desired molecule could provide therapeutic effect for a particular cardiovascular disease or condition in a patient *in vivo*.

The sufficient amount of desired molecules encoded by different genes for providing therapeutic effect in a patient *in vivo* for a particular cardiovascular disease or condition could vary dramatically because of different functions of the desired molecules and the targeted cardiovascular disease or condition. The state of the prior art of gene therapy *in vivo* was not well developed and was highly unpredictable at the time of the invention. Gene therapy protocols using nucleotide sequences encoding different proteins differ from each other because different proteins have different biological functions and their stabilities inside cells and corresponding disease to be treated could vary. In addition, different diseases differ from each other pathologically and they require nucleic acids encoding different proteins for treatment. Therefore, gene therapy using nucleotide sequences encoding different proteins or antisense RNA for various diseases has to be considered case by case. A successful gene therapy protocol can not be extrapolated into a successful result for another gene therapy protocol. For example, a successful gene therapy protocol using rAAV vector expressing FGF to treat a particular cardiovascular disease via introcoronary injection of said rAAV vector does not mean that using said rAAV vector via other administration routes or using a rAAV vector expressing protein other than the FGF via any administration route for gene therapy in vivo would also be successful. Thus, the claimed invention of the present application would not be a routine experimentation, but rather it requires one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the specification teaches that angiogenic factors and other proteins useful in the claimed method can be secreted from cardiomyocytes and exert their effects in the heart or other locations in the body so as to treat a cardiovascular condition or disease. Applicants further argue that antisense nucleic acids and protein encoding nucleic acids would be expressed in the cardiomyocytes according to the claim ed method, and there are uses other than treating cardiovascular disease or condition for the claimed method (amendment, p. 9). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and the reasons set forth above. As discussed above, the specification states "The ability to stably and efficiently program recombinant gene expression in cardiomyocytes facilitates gene therapy approaches for a variety of cardiovascular disease and conditions" and "The present invention is directed to a method of treating a cardiovascular condition by infusing an rAAV vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably efficient transduce the cardiomyocytes perfused to the artery or sinus" (see specification, page 1, 3). The claims read on gene therapy *in vivo* for a variety of cardiovascular diseases and conditions in light of the original presentation of the specification. The specification must provide sufficient enabling disclosure to support the claimed method but fails to do so. In addition, those uses other than gene therapy in vivo of the claimed method were recited in the amendment filed 3-24-03 but not in the originally filed specification, the current arguments are concerning enablement of gene therapy in vivo in light of the specification. Therefore, those other uses of the claimed method recited in the amendment filed 3-24-03 are irrelevant to the present enabling rejection under 35 U.S.C. 112 first paragraph.

Applicants cite references Aikawa et al., and Kawada et al., and argue that the claimed method can be used for purpose other than gene therapy in vivo, such as evaluating the regulation and expression of gene in the functioning heart (amendment, p. 10). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and the reasons set forth above. As discussed above the claims read on gene therapy *in vivo* for a variety of cardiovascular diseases and conditions in light of the original presentation of the specification. The specification must provide sufficient enabling disclosure to support the claimed method but fails to do so. In addition, those uses other than gene therapy in vivo of the claimed method were recited in the amendment filed 3-24-03 but not in the originally filed specification, the current arguments are concerning enablement of gene therapy in vivo in light of the specification. Therefore, those other uses of the claimed method recited in the amendment filed 3-24-03 are irrelevant to the present enabling rejection under 35 U.S.C. 112 first paragraph.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 24, 32, 33, 40, 43 and 45 remain rejected under 35 U.S.C. 102(a) as being anticipated by Hammond et al., 1998 (WO 98/50079) and is repeated for the reasons set forth in the preceding Official action mailed 9-10-03. Applicant's arguments filed 2-9-04 have been fully considered but they are not persuasive.

Applicants argue that Hammond only teaches a certain number of viral particles are delivered no matter what type of animal receives the dosage and suggests the exact dose to be administered is determined by the clinician, and Hammond only provides data for adenovirus transduction not rAAV (amendment, p. 11). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and because Hammond teaches administering 1.5×10^{12} adenovirus particles to Yolkshire domestic pig via intracoronary injection (e.g. p. 55, 63). The pig can weigh from 50kg to 150kg, the amount of the adenovirus particles administered to the pig is 1.0×10^{7} to 3×10^{7}/gm, which is in the range of $1x10^{5}$ to $1x10^{9}$ IU/gm, $1x10^{7}$ IU/gm, or $1x10^{6}$ to $1x10^{8}$ IU/gm body weight. Hammond teaches a method for treating patient with congestive heart failure by delivering a virus vector, such as rAAV vector, expressing FGF or VEGF to said patient via direct intracoronary injection of said vector into coronary artery in an amount of virus of 10^{6}-10^{14} particles or 10^{8}-10^{12} particles (see page 69, claims 26 and 28-30). If a patient's, such as pig's, average body weight is 60 kg, i.e. 60000gm, the amount of AAV virus injected to each patient would be 17 to $1.7x10^{9}$ particles/gm body weight or 1.7×10^{3} to $1.7x10^{7}$ particles/gm body weight. Therefore, Hammond not only discloses the range of virus particle used but also provides specific dosage of adenovirus particle used in pigs, such as 1.5×10^{12} adenovirus particles per Yolkshire domestic pig. Although in the example Hammond only provides the dosage used for adenovirus particle, however, in claims 26 and 28-30 Hammond not only teaches delivering adenovirus vector but also teaches delivering the recited dosage of rAAV virus vector expressing FGF or VEGF to a patient. Thus, claims 24, 32, 33, 40, 43 and 45 remain anticipated by Hammond.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 24-30 and 35-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., 1998 (WO 98/50079) and is repeated for the reasons set forth in the preceding Official action mailed 9-10-03. Applicant's arguments filed 2-9-04 have been fully considered but they are not persuasive.

Applicants reiterate the arguments regarding 35 U.S.C. 102(a) rejection and argue that it was unexpected for the amount of rAAV vector per gram body weight that leads to efficient and stable transduction of the vector into cardiomyocytes (amendment, p. 12). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and the reasons set forth above. Hammond not only teaches using a range of virus particle used but also

teach a specific amount of virus particles, such as 1.5×10^{12}, used for gene delivery via intracoronary injection.

Applicants argue that obvious to try is not a standard for the determination of obviousness under 35 U.S.C. 103 and argue that Kaplitt teaches using 10^7 rAAV particles and only 0.2% transduction efficiency obtained (amendment, p. 12). This is not found persuasive for the reasons set forth in the preceding Official action mailed 9-10-03 and because the amount of rAAV Kaplitt used is much lower than the amount of rAAV used in the present invention and the transduction efficiency of the cardiomyocytes is much lower than what is claimed in the present invention. Since Hammond suggests using 10^8-10^{12} rAAV particles, about 1.7×10^3 to 1.7×10^7 particles/gm body weight of pig, and specifically teach using 1.5×10^{12} adenovirus particles per Yolkshire domestic pig, one of ordinary skill in the art at the time of the invention would have been motivated to use 10^8-10^{12} rAAV particles as taught by Hammond for transduction of cardiomyocytes because when lower dosage of rAAV particles results in lower transduction efficiency one would use higher dosage of rAAV particles and expect higher transduction efficiency would be obtained. Thus, the dosage and time of the rAAV vector as claimed in the present invention would be obvious for one of ordinary skill in the art at the time of the invention according to the teachings of Hammond.

Conclusion

No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Shin-Lin Chen